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NON-GONOCOCCAL URETHRITIS*

BY

GEORGE W. CSONKA

St. Mary's Hospital, London

Non-gonococcal urethritis in the male and conditions customarily associated with this disorder present problems of considerable magnitude which have so far proved refractory to a satisfactory solution. The aetiology remains unknown in most cases and this has resulted in difficulties when assessing treatment and prognosis and has cast doubts on the value of epidemiological studies. It is the purpose of this paper to describe some recent trends in the investigation and management of this condition.

Non-gonococcal urethritis includes a number of entities in which a cause is identifiable such as *Trichomonas vaginalis*, fungi, and mechanical and chemical irritants. These and other well-defined types form only a small proportion of the whole group and are not further discussed. The bulk of non-gonococcal urethritis with an unknown aetiology is generally regarded to be a venereally transmitted infection. Boyd, Csonka, and Oates (1958) studied the case histories of 200 patients with first attacks of non-gonococcal urethritis and compared the data with those of an equal number of cases of gonorrhoea in men. The group with gonorrhoea showed a uniform pattern as regards incubation period, clinical symptoms, and sexual habits. This was not the case in non-gonococcal urethritis where, for example, a substantial minority (23 per cent.) denied extramarital intercourse within three months of onset of symptoms and in the others the period between intercourse and onset of urethritis varied widely. Such a finding could be expected if non-gonococcal urethritis were composed of several aetiologically distinct conditions including some of non-venereal origin. Burgess (1959) examined 250 female sexual contacts of non-gonococcal urethritis and found that two-thirds complained of vaginal discharge, in some of whom *Trichomonas vaginalis*, "non-specific" cervicitis, or cervical erosions were present. In the remaining third no clinical or bacteriological abnormalities were found and it was concluded that the male consorts of these women must have been suffering from non-venereal non-gonococcal urethritis.

It might be misleading to attach too great an importance to clinical findings in women as a similar lack of naked-eye evidence of inflammation is not uncommon in the presence of gonorrhoea. Rosedale (1959) investigated 150 consecutive female contacts of males with non-gonococcal urethritis and noted an absence of genital inflammation in two-thirds, yet, from his experience he finds it difficult to imagine that non-gonococcal urethritis in the male is not in some way related to sexual intercourse. He suggests that the relatively high incidence of this condition in married men who deny extra-marital contact and the considerable recurrence rate imply a mechanism which is more complicated than a straightforward transmission of an infective agent.

Since 1951 the Ministry of Health has published incidence figures for non-gonococcal urethritis showing a steady rise in this country over the past 10 years which is even more marked than that of gonorrhoea (Fig. 1) (Willcox, 1962; King, 1964). If, instead of annual returns, the quarterly returns are used, a new and striking feature becomes apparent: both gonorrhoea and non-gonococcal urethritis share the same incidence swing within the year—namely, a periodic increase in summer and a decrease in winter (Fig. 2). This points to similar epidemiological factors operating in both conditions, and the most plausible one appears to be that both diseases are sexually transmitted.

In a study by Morrison (1963) in Sheffield, non-gonococcal urethritis was more than twice as common among white men as among coloured immigrants, while the reverse was true with gonorrhoea. He believes that the more promiscuous immigrant is running a greater risk of contracting gonorrhoea when there is a higher incidence of this disease in the community. This might explain the increase of gonorrhoea in coloured immigrants

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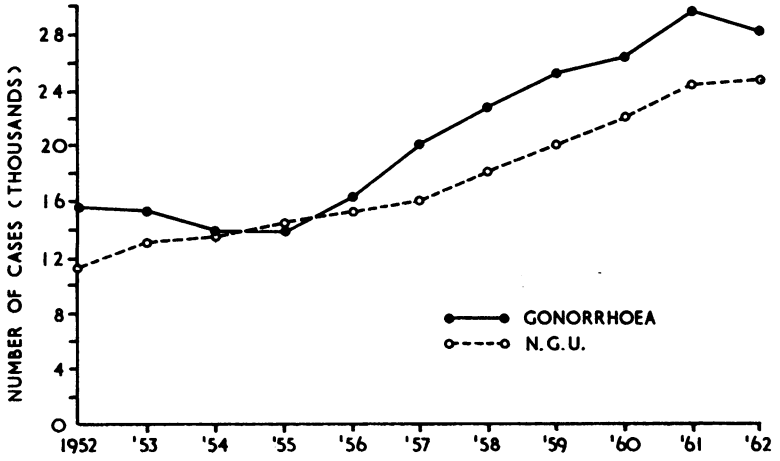

FIG. 1.—Incidence of gonorrhoea and non-gonococcal urethritis in males in England and Wales according to the annual returns of the Ministry of Health.

compared with men born in the United Kingdom but it does not explain why the incidence of non-gonococcal urethritis is significantly lower in the immigrant group. It might be that the main difference lies in the type of sexual partner in the two groups, or that there are differences in the degree of susceptibility to non-gonococcal urethritis, or perhaps that the coloured immigrant is less likely to seek medical advice with minimal non-gonococcal urethritis than the white patient. Further investigations of this type, taking into account as many parameters as possible, should prove of interest.

Published Investigations

While uncertainties of aetiology are limiting the number of epidemiological studies, the volume of published investigations into the origin of non-gonococcal urethritis is steadily increasing and selected papers representing different lines of thought are briefly discussed.

Viruses

The search for a virus aetiology was prompted by the lack of success in finding bacterial causes for what appeared to be an infection and by the discovery of inclusion bodies in urethral cells of some men with non-gonococcal urethritis (Lindner, 1910; Fritsch, Hofstätter, and Lindner, 1910). The incidence of this "inclusion-urethritis" is believed to be small, with estimations varying between 3 and 5 per cent. of all cases of non-gonococcal urethritis (Thygeson, 1954; Durel and Siboulet, 1954; Freundt, 1956). The idea of Lindner's that the agent causing trachoma was also responsible for inclusion-urethritis, cervicitis, and conjunctivitis has been recently revived with great success when it was found that contacts of one condition could develop one of the other diseases in this group and that experimental infection with the virus isolated from trachoma could produce inclusion-conjunctivitis (Gear, Gordon, Jones, and Bell, 1963). These workers proposed that a new

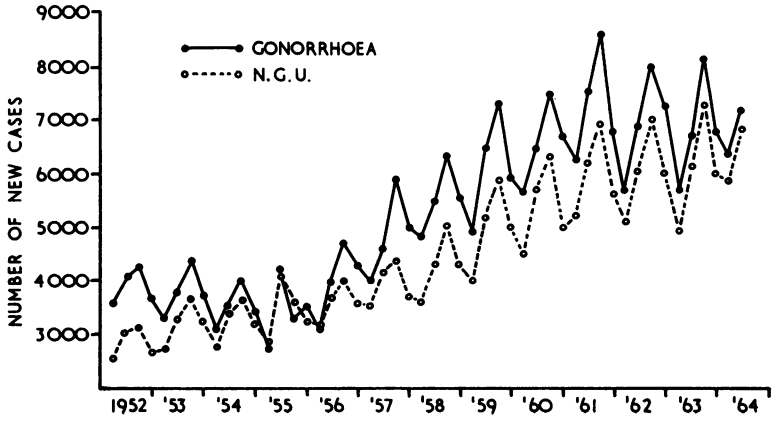

FIG. 2.—Incidence of gonorrhoea and non-gonococcal urethritis in males in England and Wales according to the quarterly returns of the Ministry of Health.

communal name for the isolates from trachoma and inclusion-conjunctivitis should be compounded from the first letters of the old ones—namely, TRIC virus (*TR*achoma *I*nclusion *C*onjunctivitis virus). Jones and his associates isolated TRIC virus from a few men with inclusion-urethritis, thus opening the way for further study of its significance in genital infection (Jones, 1964; Dunlop, Jones, and Al-Hussaini, 1964). Siboulet and Galistin (1962a, b) claim to have isolated a virus from the urethra of five patients with Reiter's syndrome and have called it "chlamydozoon oculogenitale". They suggested that the organism, which they propagated in yolk-sac culture, was the virus of inclusion-conjunctivitis/urethritis. Immunofluorescence methods were also tried by these workers for the more rapid diagnosis of this virus with apparent success in two cases (Siboulet, Galistin, and Huriez, 1962). It is felt that insufficient evidence for their claim of identification was offered and no mention was made of what precautions were taken to exclude pleuropneumonia-like organisms from their preparations, as it is known that these organisms can be carried as a contaminant in fertilized eggs and of course also be present in urethral cells.

Members of the inclusion-conjunctivitis group of viruses are susceptible to broad-spectrum antibiotics and in this as in other important aspects, such as the presence of DNA *and* RNA in the organism, they differ from all other viruses. Some authorities therefore regard them as intracellular bacterial agents rather than true viruses.

With the exception of the chlamydozoon oculogenitale/TRIC virus isolations from a handful of patients with non-gonococcal urethritis and Reiter's syndrome, other recent attempts to isolate a virus from the urethral discharge of such cases have been unsuccessful (Ford, 1956, 1958; Csonka and Furness, 1960; Whittington, 1962; Claus, McEwen, Brunner, and Tsamparlis, 1964; Morton, Gillespie, and Wilson, 1964). Whittington in her discussion states that the failure to grow virus is unlikely to be due to a defect in the systems employed as she was able to grow virus from other sources using the same cultures and techniques. It may be that the cell-types used were unsuitable for the isolation of virus inhabiting the urethra, or that growth conditions were not optimal, or perhaps that virus was growing in the cells without giving any evidence of its presence. It is, however, just as likely that a specific virus is not the cause of the majority of non-gonococcal urethritis. One of the facts which has to be accounted for is the rapid clinical improvement on broad-spectrum antibiotics of 75 to 80 per cent. of patients with non-gonococcal urethritis, and apart from the trachoma/LGV group of viruses no others are known to be susceptible to these drugs. For a variety of reasons the reviewer feels that TRIC or allied viruses are not the cause in the great majority of cases and one may have to look elsewhere than among the viruses for the aetiology of non-gonococcal urethritis.

Pleuropneumonia-like Organisms (PPLO)—Mycoplasma

PPLO are a group of filterable pleomorphic organisms which lack a rigid cell wall. The smallest viable elements are equivalent in size to the larger viruses. Dienes and Edsall (1937) were the first to demonstrate PPLO from the human genital tract. Since then genital strains of PPLO have been found in a proportion of normal individuals and in a higher proportion of patients with genito-urinary inflammation such as haemorrhagic cystitis, non-gonococcal urethritis, cervicitis, etc. Klieneberger-Nobel (1959) found that under optimal conditions PPLO could be grown in 48 per cent. of cases of non-gonococcal urethritis, in 30 per cent. of cases of gonorrhoea, and in 3 per cent. of healthy men. Other investigators obtained either a lower isolation rate in non-gonococcal urethritis or found that the differences between the groups with urethritis and controls were less marked (Nicol and Edward, 1953; Wagner, Morse, and Kuhns, 1953; Freundt, 1956; Ford, Rasmussen, and Minken, 1962). There is, however, general agreement that the frequency of positive isolations of PPLO from the genital tract is higher in women than in men and the highest isolation rate of all is in women with an inflamed urogenital tract where up to 90 per cent. of PPLO were isolated (Klieneberger-Nobel, 1959). The literature which has accumulated on the significance of PPLO in human urogenital disease is voluminous, and little would be gained by compiling a catalogue of papers as the conclusions so often contradict each other. An exception will be made with two articles which seem to have escaped attention and report rather unusual findings: Kuzell and Mankle (1960) described how one of their male laboratory technicians, while working with a PPLO culture from a patient with Reiter's syndrome, developed non-gonococcal urethritis and conjunctivitis and from both lesions PPLO could be isolated. He recovered rapidly on aureomycin but after resuming the same work in the laboratory his symptoms recurred and once again PPLO were grown. The authors suggested that this is an instance of accidental laboratory infection with PPLO and imply that this organism is responsible for the genital infection underlying Reiter's syndrome. The second paper

is by Kritschevskij (1954) from Russia who investigated 17 cases of Reiter's syndrome and found organisms which he regarded as PPLO associated with the urethral epithelial cells in 14 patients. The organisms were cultured and inoculated into the anterior chamber of the eye of rabbits. All the animals developed uveitis and one urethritis. Mice were then inoculated intraperitoneally with a filtered suspension from the infected rabbit eye and they developed bilateral conjunctivitis, polyarthritis, and abscess formation.

The findings in both papers are remarkable and at variance with the results of other workers; they will, therefore, need most careful critical appraisal, particularly as difficulties and misinterpretations are disappointingly common in clinical and experimental work on PPLO.

In support of PPLO being a cause of non-gonococcal urethritis it is sometimes quoted that PPLO are most sensitive to tetracycline, moderately sensitive to chloramphenicol and streptomycin, and insensitive to sulphonamides and penicillin, which is in fairly good accord with the therapeutic response of non-gonococcal urethritis to these drugs, but, as King (1964) points out, good clinical results have also been reported with erythromycin and oleandomycin, to which PPLO are insensitive (Blyth, 1958). During current work by the reviewer antibiotic sensitivity of PPLO isolated from non-gonococcal urethritis has shown important variations from that reported by Blyth and a study to relate *in vitro* sensitivity to clinical therapeutic results is in progress.

The reviewer's own feeling about the significance of PPLO in non-gonococcal urethritis and associated diseases is that there is not enough evidence to commit oneself one way or the other. It can be said with some assurance that even if PPLO should be found to be a cause of non-gonococcal urethritis it is not likely to be a common cause.

T-forms of PPLO

In 1954 Shepard isolated from the urethral discharge of non-gonococcal urethritis minute organisms producing tiny colonies on special culture media and named them T-forms (T for tiny) of PPLO. Evidence that these organisms belong to the group of mycoplasma is considered to be incomplete by several authorities. Ford (1962) confirmed the work of Shepard and appears to have achieved continuous propagation of this extraordinarily fastidious organism. Ford and Macdonald (1963) isolated "ordinary" large-colony PPLO in 27 per cent. of patients with non-gonococcal urethritis and considered these to be aetiologically irrelevant against 79 per cent. of T-form PPLO which they claimed to be *the* causative agent. The T-form PPLO is susceptible to tetracycline just as is the large-colony PPLO. Both types were also found by these investigators in a small number of apparently healthy individuals. It is noteworthy that only a few authorities have been able to grow the small-colony PPLO and none have obtained the 70 to 80 per cent. of positive isolations in non-gonococcal urethritis found by Shepard and Ford. Claus and others (1964) suggest that the reason for this may be due to differences in the selection of patients, as it has been shown that the isolation rate of PPLO increases with the degree of promiscuity of the population sample examined. As this applies to both types of organisms it would not explain the different findings reported in the literature. The reviewer fully agrees with King (1964) who calls for more proof before the T-strain can be regarded as a PPLO and further assessment before this organism can be regarded as a major cause of non-gonococcal urethritis.

L-forms of Bacteria

Colonies closely resembling PPLO have been discovered growing in pure cultures of a variety of bacteria by Klieneberger-Nobel (1935) at the Lister Institute and she called these L-forms (L for Lister). In most instances L-forms appeared only under the influence of chemicals or antibiotics which damaged or removed the cell wall of the bacterium—for example, penicillin. Some L-forms of bacteria are antigenically related to parasitic PPLO but the exact relationship is obscure and Klieneberger-Nobel is now firmly of the opinion that PPLO and L-forms of bacteria are entirely separate entities. It has been suggested that L-forms represent a part in the bacterial growth cycle in their natural environment and are not just a product depending on special conditions in artificial media. There is no proof of this, and the technical difficulties in relation to this problem are formidable; however, the hypothesis has been put forward by Harkness (1950) and others that PPLO found in the genital tract in non-gonococcal urethritis may be an L-form of certain bacteria including occasionally the gonococcus. If this theory were confirmed it would give unexpected unity to a number of apparently unconnected bacteriological findings. In a recent paper by Dienes, Bandur, and Madoff (1964) the development of L-forms was demonstrated in several strains of gonococci on ordinary media without exposure to agents known to induce such transformation. A suggestion of a growth cycle which included the L-form was obtained but could not be definitely proven as further cultivation in transfer was not successful.

As L-forms of bacteria are insensitive to penicillin

it seems that two types of cases might be especially worth investigating for the existence of gonococcal L-forms: (1) cases of penicillin-resistant gonorrhoea and (2) cases of gonorrhoea which respond to penicillin with the disappearance of gonococci from the discharge but which continue to have non-gonococcal urethritis or develop it within a few days after apparently successful treatment of gonorrhoea. A search for the presence of L-forms of bacteria in nature is likely to prove extremely difficult and one should not expect a ready answer in our field for some time to come.

Other Bacteriological Studies

Ordinary culture media have been of little value, as either no growth was obtained or organisms believed to be commensals only were found. Such organisms have been isolated from healthy controls and were present both before and after successful treatment of non-gonococcal urethritis (Ambrose and Taylor, 1953; Willcox, 1953; Röckl and Nasemann, 1959). Ambrose, Taylor, and Josefiak (1961) believe that the inability to grow bacteria from the urethra reported by others might be due to the use of unsuitable culture media. Since efforts to incriminate viruses and PPLO as a major cause of non-gonococcal urethritis have not met with much success so far and since broad-spectrum antibiotics have a measurable effect in this condition, it may be useful to re-examine the role of "ordinary" bacteria with the help of new bacteriological techniques and improved culture media.

Psychological Factors

Siboulet (1960a) stated that more than half of his patients with non-gonococcal urethritis needed some form of psychotherapy and that the common disturbance in chronic cases was depression. He thought that the tortuous course of urethritis was responsible for this. Elsewhere (1960b) he reported that, of 6,000 men with urethritis of all types, 20 per cent. had "insignificant secretion and urethrophobia". Though the figures given in these two papers may differ greatly from those found in other parts of the world, they illustrate the two relevant psychological problems, primary urethrophobia and secondary psychological stress and strain, developing in the course of non-gonococcal urethritis particularly in chronic cases and in temperamentally predisposed individuals. The reviewer sometimes finds it impossible to distinguish between the two types if the patient is seen for the first time after a period during which he has had repeated antibiotic therapy and a variety of investigations with equivocal results. The management of these cases remains unsatisfactory.

While investigations into the aetiology of non-gonococcal urethritis are receiving most of the attention, there have been recent studies of associated clinical features such as urethral stricture and chronic prostatitis which will be briefly discussed. Reiter's syndrome is outside the scope of this review.

Urethral Stricture

Stephenson (1956) found urethral stricture in 5 per cent. of 243 men with recurrent urethritis, mostly of the non-gonococcal type. Hancock (1959) noted from the records of 276 patients with non-gonococcal urethritis that routine urethroscopy revealed stricture in 4·7 per cent., but some of these patients had suffered from gonorrhoea in the past. Dunlop (1961) found urethral stricture in 4·9 per cent. of 328 patients. A previous history of urethritis was common in cases with urethral stricture and had usually been treated with modern methods. Only four of the total of 36 patients with a stricture complained of symptoms of urinary obstruction. This was thought to be due to the relative youth of the men, most of whom were under 40 years of age, which might not have allowed sufficient time to pass for obstruction to become manifest. It is also possible that post-urethritic strictures are less severe or in some way different from post-gonococcal ones, and it is noteworthy in this connexion that Dunlop found more than half of the strictures proximal to the bulb whereas the commonest site for post-gonococcal strictures is in the bulbous urethra. If, as suggested, strictures develop in about 5 per cent. of patients with non-gonococcal urethritis despite antibiotic treatment, we should have recognized many instances of urethral obstruction from this cause and as there is little evidence for this it seems likely that these strictures are not usually obstructive. It is also possible that some of the strictures detected were congenital, traumatic, or caused in some other way and were associated by chance with non-gonococcal urethritis or alternatively, that the presence of a urethral stricture from whatever cause may have been a factor favouring the establishment of non-gonococcal urethritis.

Chronic Prostatitis

There is no universally accepted diagnostic test for chronic prostatitis but the differences which divide authorities are a matter of detail rather than of principle. There is a much more fundamental difference of opinion on the significance of chronic prostatitis in relation to anterior uveitis, Reiter's syndrome, and ankylosing spondylitis.

The most widely practised method of diagnosing the commonly symptomless prostatitis is by counting the leucocytes in the expressed prostatic fluid per 1/12th microscopic field and dividing the normal from the abnormal according to an arbitrary figure. It is largely this value which varies with different investigators and makes comparisons difficult. The variability of these counts when repeated in the same individual, the poor correlation of "abnormally" high counts with prostatic inflammation diagnosed by other means, and the finding of high counts in otherwise entirely normal men has led several authors, particularly in the USA, to regard the test as valueless (O'Shaughnessy, Parrino, and White, 1956; Parrino, 1958; Gartman, 1958). This is considered to be too pessimistic, especially as there are some indications that the test itself can be made more reliable and accurate. Efforts in this direction have already been made by Huggins and McDonald (1944) and Oates (1958). The former estimated the total number of leucocytes in a prostatic fluid specimen but gave no details of the method used. In their brief communication it was stated that patients suffering from chronic prostatitis had leucocyte counts of 1,200 to 13,000 per cubic millimetre; the normal values were between 200 and 1,000 cells per cubic millimetre. Oates dismissed total counts as time-consuming and inaccurate and suggested that five preparations from the same prostatic fluid specimen should be routinely examined and a diagnosis of chronic prostatitis be made on finding ten or more leucocytes per 1/12th field in any one preparation. In the reviewer's experience this modification does help eliminate some errors inherent in single examinations; it is felt, however, that if a reasonably accurate method for total count became available it would greatly improve the test. With this in mind, methods for counting leucocytes in prostatic secretions are being investigated at present with promising results. The technique and findings will be the subject of a forthcoming paper.

Even if this or some other modification of the prostatic secretion test should prove successful, a great deal of work remains to be done on the role of physiological factors such as the age of the patient and sexual activity preceding the test and other factors which might be expected to influence the results when compiling the range of normal values. Some form of standardized prostatic test would facilitate the evaluation of abnormally high counts in patients with uveitis, Reiter's disease, and ankylosing spondylitis on which opinions differ widely at present. As a long-term study it is suggested that the possible association of chronic prostatitis with local disease of the prostate such as benign hypertrophy, prostatic calculi, and, above all, carcinoma of the prostate should be looked into.

Treatment

Non-gonococcal urethritis with its tendency to spontaneous remissions and recurrences and no demonstrable cause poses problems in the assessment of treatment. Much effort seems to have been wasted on therapeutic trials which were not controlled and where insufficient clinical data were given to permit critical conclusions and comparisons to be made. In this situation double-blind trials are the best way to show convincingly the effect of treatment and should only be dispensed with if the therapeutic response is immediate and approaches 90 to 100 per cent. efficacy. None of the antibiotics investigated belong to this class, though the tetracycline group of drugs comes close to it. When assessing results of treatment it is customary to do so at the end of three months. This fairly long observation period is notoriously difficult to achieve in a sufficient proportion of patients to satisfy the medical statistician, and in the writer's opinion may allow the introduction of other factors which can bias the results. It is suggested that early evaluation of a drug—say one or two weeks after treatment—is preferable for these reasons: it is generally agreed that in patients in whom treatment is successful the response is immediate; during the short period of observation recommended the defaulter rate is usually low enough to allow the collection of a statistically acceptable series; and difficulties in the interpretation of treatment failure due to re-infection are less likely to arise early on. It is not suggested that early assessment is ideal as the genuine late relapse will be missed, but it is believed that in present circumstances it offers the least biased estimate of therapeutic response. In Fig. 3 treatment results of authors using a placebo (sometimes in a double-blind trial) are shown together with representative results for broad-spectrum antibiotics, mostly tetracyclines. In the first weeks after treatment there is a highly significant difference between the response rate to placebo and antibiotic. At the end of the customary observation period this difference is less marked though still significant. The cure rate after broad-spectrum antibiotics is similar throughout the observation period and there seems to be no advantage in waiting beyond the first week or two to assess these results. In patients receiving a placebo one can detect progressive improvement, which is presumably a reflection of the natural cure rate of non-gonococcal urethritis.

Two therapeutic trials with different results from the others are also shown. One is by Fowler (1958)

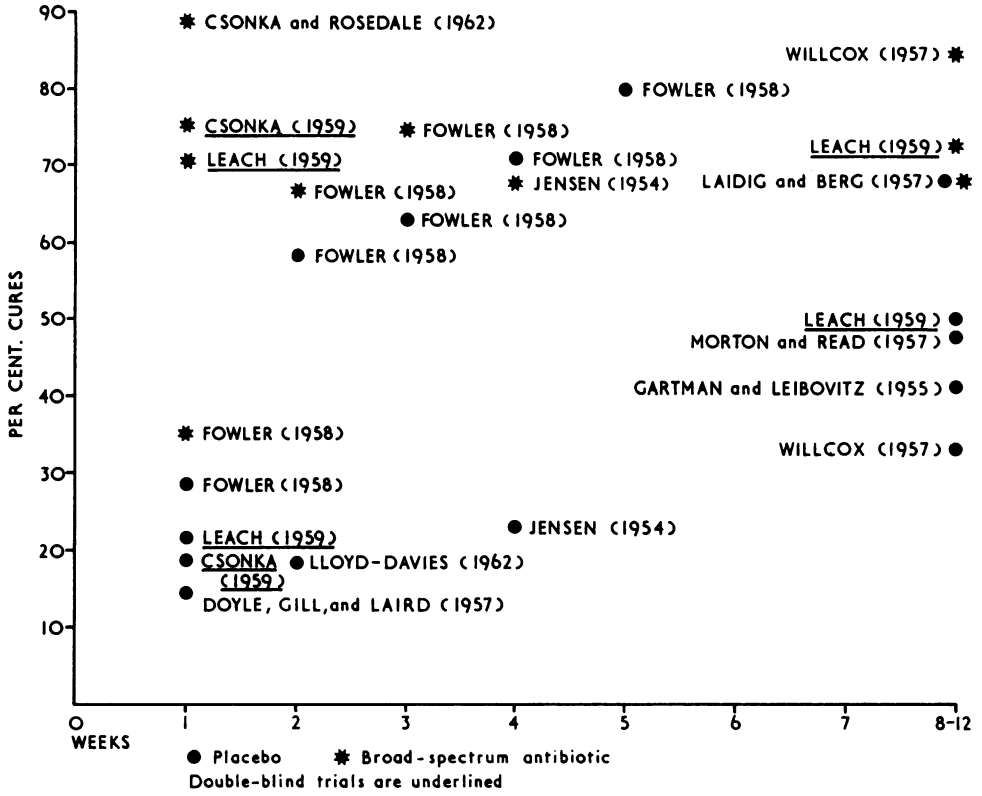

FIG. 3.—Cure rate of non-gonococcal urethritis after treatment with placebo and broad-spectrum antibiotics by various authors.

who obtained quite a high cure rate early on with potassium citrate alone, which he regarded as a placebo; his results with terramycin were only little better. This paper is open to criticism on the ground that it is a retrospective study, that the patients were selected from a larger unspecified case material, and that the author preferred potassium citrate to other forms of treatment. The second trial by Laidig and Berg (1957) showed equally favourable responses to placebo, chlortetracycline, and other drugs. Once again, patients were selected, which makes interpretation of the results most difficult.

Unlike the trials with tetracycline and other broad-spectrum antibiotics which gave broadly similar results, trials with sulphonamides (short, medium, and long-acting), streptomycin, and combinations of these drugs resulted in a great number of conflicting reports. If one assumes that these drugs have a comparatively weak effect in non-gonococcal urethritis, variations and defects in the trials would be more critical than when more potent antibiotics are used. It is unfortunate that no satisfactory double-blind trials with sulphonamides, streptomycin, or combinations of these drugs have been reported and it is likely that the optimal time for such studies has passed as the interest is shifting towards the more active broad-spectrum antibiotics.

Finally, the recent introduction of narrowly specific drugs such as metronidazole (Flagyl) and antiviral agents claimed to be effective against particular viruses or groups of viruses has led to therapeutic trials in non-gonococcal urethritis—alas, with negative results. In the absence of a fully effective treatment every new drug offering a chance of success should be tried and even negative findings are well worth recording as they will help to define the therapeutic sensitivity pattern of non-gonococcal urethritis, which might prove of value in the search for its aetiology.

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